



## DEPARTMENT OF JUSTICE

### Drug Enforcement Administration

#### 21 CFR Part 1310

[Docket No. DEA-951]

#### Designation of 4-Piperidone as a List I Chemical

**AGENCY:** Drug Enforcement Administration, Department of Justice.

**ACTION:** Notice of proposed rulemaking.

**SUMMARY:** The Drug Enforcement Administration is proposing the control of 4-piperidone, its acetals, its amides, its carbamates, its salts, and salts of its acetals, its amides, and its carbamates, whenever the existence of such is possible, as a list I chemical under the Controlled Substances Act. The Drug Enforcement Administration finds that 4-piperidone is used in the illicit manufacture of the controlled substance fentanyl, and is important to the manufacture of the controlled substance fentanyl because it cannot be replaced by other chemicals in its respective synthetic pathways which are used in the illicit manufacture of fentanyl. If finalized, this action would subject handlers of 4-piperidone to the chemical regulatory provisions of the Controlled Substances Act and its implementing regulations. This rulemaking does not establish a threshold for domestic and international transactions of 4-piperidone. As such, all transactions of chemical mixtures containing 4-piperidone will be regulated at any concentration and will be subject to control under the Controlled Substances Act.

**DATES:** Comments must be submitted electronically or postmarked on or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER]. Commenters should be aware that the electronic Federal Docket Management System will not accept any comments after 11:59 p.m. Eastern Time on the last day of the comment period.

**ADDRESSES:** To ensure proper handling of comments, please reference “Docket No. DEA-951” on all electronic and written correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration encourages that all comments be submitted electronically through the Federal eRulemaking Portal which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to <https://www.regulations.gov> and follow the online instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number for your comment. Please be aware that submitted comments are not instantaneously available for public view on *Regulations.gov*. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.

- *Paper comments:* Paper comments that duplicate electronic submissions are not necessary. Should you wish to mail a paper comment, *in lieu of* an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrisette Drive, Springfield, Virginia 22152.

**FOR FURTHER INFORMATION CONTACT:** Terrence L. Boos, Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Telephone: (571) 362–3249.

**SUPPLEMENTARY INFORMATION:**

**Posting of Public Comments**

Please note that all comments received in response to this docket are considered part of the public record. They will, unless reasonable cause is given, be made available by the Drug Enforcement Administration (DEA) for public inspection online at <https://www.regulations.gov>. Such information includes personal identifying information (such as your name, address, etc.) voluntarily submitted by the commenter. The Freedom of

Information Act applies to all comments received. If you want to submit personal identifying information (such as your name, address, etc.) as part of your comment, but do not want it to be made publicly available, you must include the phrase “PERSONAL IDENTIFYING INFORMATION” in the first paragraph of your comment. You must also place all of the personal identifying information you do not want made publicly available in the first paragraph of your comment and identify what information you want redacted.

If you want to submit confidential business information as part of your comment, but do not want it to be made publicly available, you must include the phrase “CONFIDENTIAL BUSINESS INFORMATION” in the first paragraph of your comment. You must also prominently identify the confidential business information to be redacted within the comment.

Comments containing personal identifying information or confidential business information identified as directed above will be made publicly available in redacted form. If a comment has so much confidential business information that it cannot be effectively redacted, all or part of that comment may not be made publicly available. Comments posted to <https://www.regulations.gov> may include any personal identifying information (such as name, address, and phone number) included in the text of your electronic submission that is not identified as directed above as confidential.

An electronic copy of this proposed rule is available at <https://www.regulations.gov> for easy reference.

### **Legal Authority**

The Controlled Substances Act (CSA) gives the Attorney General the authority to specify, by regulation, chemicals as list I chemicals.<sup>1</sup> A “list I chemical” is a chemical that is used in manufacturing a controlled substance in violation of the CSA and is important to the manufacture of the controlled substances.<sup>1</sup> The current list of all listed chemicals is

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<sup>1</sup> 21 U.S.C. 802(34).

published at 21 CFR 1310.02. Pursuant to 28 CFR 0.100(b), the Attorney General has delegated his authority to designate list I chemicals to the Administrator of DEA (Administrator). DEA regulations set forth the process by which DEA may add a chemical as a listed chemical. As set forth in 21 CFR 1310.02(c), the agency may do so by publishing a final rule in the Federal Register following a published notice of proposed rulemaking with at least 30 days for public comments.

## **Background**

The clandestine manufacture of fentanyl remains extremely concerning as the distribution of illicit fentanyl continues to drive drug-related overdose deaths in the United States. Fentanyl is a synthetic opioid and was first synthesized in Belgium in the late 1950s. Fentanyl was introduced into medical practice and is approved for medical practitioners in the United States to prescribe lawfully for anesthesia and analgesia. Yet, due to its pharmacological effects, fentanyl can be used as a substitute for heroin, oxycodone, and other opioids in opioid dependent individuals. Therefore, despite its accepted medical use in treatment in the United States, the DEA controls fentanyl as a schedule II controlled substance due to its high potential for abuse and dependence.<sup>2</sup>

The unlawful trafficking of fentanyl in the United States continues to pose an imminent hazard to the public safety. Since 2012, fentanyl has shown a dramatic increase in the illicit drug supply as a single substance, in mixtures with other illicit drugs (*i.e.*, heroin, cocaine, and methamphetamine), or in forms that mimic pharmaceutical preparations including prescription opiates and benzodiazepines.<sup>3</sup>

DEA has noted a significant increase in overdoses and overdose fatalities from fentanyl in the United States in recent years. According to the Centers for Disease Control and Prevention (CDC), opioids, mainly synthetic opioids (which includes fentanyl), are

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<sup>2</sup> 21 U.S.C. 812(c) Schedule II(b)(6) and 21 CFR 1308.12(c).

<sup>3</sup> United Nations Office on Drugs and Crime, Global SMART Update Volume 17, March 2017. [https://www.unodc.org/documents/scientific/Global\\_SMART\\_Update\\_17\\_web.pdf](https://www.unodc.org/documents/scientific/Global_SMART_Update_17_web.pdf).

predominantly responsible for drug overdose deaths in recent years. According to CDC data, drug-induced overdose deaths involving synthetic opioids (excluding methadone) in the United States increased from 36,359 in 2019 to 56,516 in 2020 to 57,802 in 2021 (provisional).<sup>4</sup> Of the drug overdose death data (106,854) predicted for the 12 month-ending November 2021, synthetic opioids were involved in about 65.9 percent of all drug-induced overdose deaths.<sup>5</sup> The increase in overdose fatalities involving synthetic opioids coincides with a dramatic increase in law enforcement encounters of fentanyl. According to the National Forensic Laboratory Information System (NFLIS-Drug),<sup>6</sup> reports from forensic laboratories of drug items containing fentanyl increased dramatically since 2014, as shown in Table 1.

**Table 1. Annual Reports of Fentanyl Identified in Drug Encounters.**

Year	2014	2015	2016	2017	2018	2019	2020
Reports	5,535	15,456	37,142	61,604	89,764	107,080	115,762

### **Role of 4-Piperidone in the Synthesis of Fentanyl**

Fentanyl is not a naturally occurring substance. As such, the manufacture of fentanyl requires it to be produced through synthetic organic chemistry. Synthetic organic chemistry is the process in which a new organic molecule is created through a series of chemical reactions, which involve precursor chemicals. Through chemical reactions, the chemical

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<sup>4</sup> Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Provisional Mortality on CDC WONDER Online Database. Data are from the final Multiple Cause of Death Files, 2018-2020, and from provisional data for years 2021-2022, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at <https://wonder.cdc.gov/mcd-icd10-provisional.html> on May 5, 2022.

<sup>5</sup> Ahmad FB, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2021. Accessed at <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm> on May 5, 2022.

<sup>6</sup> The National Forensic Laboratory Information System (NFLIS-Drug) is a national forensic laboratory reporting system that systematically collects results from drug chemistry analyses conducted by Federal, State and local forensic laboratories in the United States. While NFLIS-Drug data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. See 76 FR 77330, 77332 (December 12, 2011). NFLIS-Drug data was queried on January 13, 2022.

structures of precursor chemicals are modified in a desired fashion. These chemical reaction sequences, also known as synthetic pathways, are designed to create a desired substance. Several synthetic pathways to fentanyl have been identified in clandestine laboratory settings; these include the original “Janssen method,” the “Siegfried method,” and the “Gupta method.” In response to the illicit manufacture of fentanyl using these methods, DEA controlled *N*-phenethyl-4-piperidone (NPP),<sup>7</sup> *N*-(1-benzylpiperidin-4-yl)-*N*-phenylpropionamide (benzylfentanyl) and *N*-phenylpiperidin-4-amine (4-anilinopiperidine)<sup>8</sup> as list I chemicals, and 4-anilino-*N*-phenethylpiperidine (ANPP)<sup>9</sup> and *N*-phenyl-*N*-(piperidin-4-yl)propionamide (norfentanyl)<sup>10</sup> as schedule II immediate precursors under the CSA.

In 2017, the United Nations Commission on Narcotic Drugs placed NPP and ANPP in Table I of the Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988 (1988 Convention) in response to the international reintroduction of fentanyl on the illicit drug market. As such, member states of the United Nations were required to regulate these precursor chemicals at the national level. Importantly, the People’s Republic of China regulated NPP and ANPP on February 1, 2018.<sup>11</sup>

To circumvent these regulations, illicit fentanyl manufacturers continue to employ unregulated precursor chemicals in the illicit synthesis of fentanyl. Recent law enforcement information indicates that illicit fentanyl manufacturers may be utilizing precursor chemicals that serve as precursors to those precursor chemicals already controlled, sometimes referred to as “pre-precursors.” 4-Piperidone (also, known as, piperidin-4-one) serves as a precursor chemical for the previously controlled list I chemicals involved in many synthetic routes to

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<sup>7</sup> 72 FR 20039 (April 23, 2007).

<sup>8</sup> 85 FR 20822 (May 15, 2020).

<sup>9</sup> 75 FR 37295 (August 30, 2010).

<sup>10</sup> 85 FR 21320 (May 18, 2020).

<sup>11</sup> <https://www.dea.gov/press-release/2018/01/05/china-announces-scheduling-controls-two-fentanyl-precursor-chemicals>. Accessed March 9, 2022.

fentanyl; it is used to make NPP, benzylfentanyl, and 4-anilinopiperidine, all of which are list I chemicals under the CSA.<sup>12</sup>

In addition to the continuous exploration of viable precursors to manufacture fentanyl, illicit manufacturers also employ protecting group strategies on known fentanyl precursors. These protecting group strategies modify the chemical structure of a known precursor and are specifically designed to disguise the known precursor to evade law enforcement detection or to enhance the manufacturing process of the controlled substance the known precursor is used to make. These modified precursors are sometimes referred to as “masked precursors.” For example, 1-boc-4-anilinopiperidine (*tert*-butyl 4-(phenylamino)piperidine-1-carboxylate, 1-boc-4-AP), a carbamate of 4-anilinopiperidine and a list I chemical, was identified as a “masked” precursor chemical used in the illicit manufacture of fentanyl. Likewise, 1-boc-4-piperidone (*tert*-butyl 4-oxopiperidine-1-carboxylate), a carbamate of 4-piperidone, and 4,4-piperidinediol (piperidine-4,4-diol) have also been identified as “masked” precursors. As a carbamate of 4-piperidone, 1-boc-4-piperidone would be controlled as a list I chemical upon completion of this rulemaking, as proposed. Similarly, 4,4-piperidinediol (Chemical Abstract Service Registry Number (CAS RN) 73390-11-1 for the free base and CAS RN 40064-34-4 for the hydrochloride salt) is 4-piperidone with the inclusion of one water molecule of hydration and is known as a hydrate of 4-piperidone. As a hydrate of 4-piperidone, 4,4-piperidinediol would also be subject to control under the listing of 4-piperidone upon completion of this rulemaking, as proposed. These masked precursors serve both a role in attempts to evade law enforcement detection as well as a strategic synthesis advantage compared to their unprotected counterparts, namely 4-anilinopiperidine and 4-piperidone.

#### **4-Piperidone**

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<sup>12</sup> 72 FR 20039 (April 23, 2007) and 85 FR 20822 (April 15, 2020).

The original published synthetic pathway to fentanyl, known as the Janssen method, does not involve NPP or ANPP as precursor chemicals. This synthetic pathway involves the important precursors, benzylfentanyl and norfentanyl. 4-Piperidone serves as a precursor chemical to benzylfentanyl, a list I chemical under the CSA,<sup>8</sup> which is converted to norfentanyl, the schedule II immediate precursor in this synthetic pathway. Norfentanyl is then subjected to one simple chemical reaction to complete the synthesis of fentanyl. Norfentanyl is controlled in schedule II of the CSA.<sup>10</sup>

Like the Janssen method, 4-piperidone serves as an early-stage precursor chemical in the Siegfried method. 4-Piperidone is a precursor to NPP, a known fentanyl precursor and list I chemical, in the Siegfried method. NPP, a list I chemical under the CSA,<sup>7</sup> is then converted to ANPP, the schedule II immediate precursor in this synthetic pathway. ANPP is then subjected to a simple one step chemical reaction to complete the synthesis of fentanyl. ANPP is controlled as a schedule II immediate precursor under the CSA.<sup>9</sup>

In addition to the Janssen and Siegfried methods, clandestine manufacturers are using other methods to synthesize fentanyl, one of which is known as the Gupta method. 4-Piperidone can be used to synthesize 4-anilinopiperidine, a list I chemical under the CSA<sup>8</sup> and key precursor in the Gupta method. 4-Anilinopiperidine serves as an alternative precursor chemical to NPP in the synthesis of ANPP, albeit through a different synthetic process. The resulting ANPP is then used as the immediate precursor chemical in the illicit manufacture of the schedule II controlled substance, fentanyl.

DEA has determined that 4-piperidone is commercially available from both domestic and foreign suppliers. DEA is aware of at least 38 domestic suppliers and 19 foreign suppliers. 4-Piperidone is attractive to illicit manufacturers due to the lack of regulations on this chemical, it is readily available from chemical suppliers, and it can be easily converted to known fentanyl precursors, including NPP, benzylfentanyl, and 4-anilinopiperidine.



4-Piperidone and 1-boc-4-piperidone have been imported and identified in law enforcement encounters in the United States. According to law enforcement information, between March 2016 and October 2021, there have been three seizures of 4-piperidone (2) and 1-boc-4-piperidone (1) totaling 357 kilograms (kg) at ports of entry in the United States. In addition to these encounters, a query of DEA's Laboratory Information Management System (LIMS) resulted in three domestic reports of 4-piperidone (1) and 1-boc-4-piperidone (2) from analyses conducted on submitted drug evidence by DEA forensic laboratories. 4-Piperidone was also identified at clandestine laboratories located in Arizona and Pennsylvania, which were involved in the illicit manufacture of fentanyl.

As of May 2019, in addition to domestic encounters, the International Narcotics Control Board of the United Nations reported eight international transactions of 4-piperidone (6) and 1-boc-4-piperidone (2) through the Precursors Incident Communication System (PICS)<sup>13</sup> reporting system. These incidents reported to PICS totaled approximately 1,900 kg and had destinations located in North America and Europe. Along with the incidents reported to PICS, DEA is aware of ten additional seizures of 4-piperidone (9) and 1-boc-4-piperidone (1) at international ports of entry since May 2019, totaling approximately 1,335 kg.

These recent law enforcement encounters of 4-piperidone coincide with the placement of NPP and ANPP in Table I of the 1988 Convention, the People's Republic of China regulating NPP and ANPP as of February 1, 2018, and the regulation of benzylfentanyl and 4-anilinopiperidine as list I chemicals and the designation of norfentanyl as a schedule II immediate precursor to fentanyl in the United States. The domestic and international encounters of 4-piperidone at ports of entry and the identification of 4-piperidone at domestic fentanyl clandestine laboratories indicate a change in illicit fentanyl

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<sup>13</sup> PICS is a platform that allows Governments to exchange operational and investigative intelligence and to generate strategic intelligence on precursors trafficking. PICS reports were collected up to December 16, 2021.

manufacturing methods in efforts to evade international controls on NPP and ANPP and additional controls on benzylfentanyl, 4-anilinopiperidine, and norfentanyl in the United States.

**Regulation of 4-Piperidone, Including Its Acetals, Its Amides, Its Carbamates, Its Salts, and Salts of Its Acetals, Its Amides, and Its Carbamates, Whenever the Existence of Such is Possible, as a List I Chemical**

The CSA, specifically 21 U.S.C. 802(34), and its implementing regulations at 21 CFR 1310.02(c), provide the Attorney General with the authority to specify, by regulation, additional precursor or essential chemicals as listed chemicals if they are used in the manufacture of controlled substances in violation of the CSA. Recent law enforcement encounters indicate 4-piperidone is being used in the illicit manufacture of the schedule II controlled substance fentanyl. This proposed rule would regulate 4-piperidone as a list I chemical because DEA finds that 4-piperidone is used in the illicit manufacture of the controlled substance fentanyl, and is important to the manufacture of the controlled substance fentanyl because it cannot be replaced by other chemicals in its respective synthetic pathways which are used in the illicit manufacture of fentanyl.

**Chemical Mixtures of 4-Piperidone**

This proposed rulemaking, if finalized, would specify that chemical mixtures containing 4-piperidone would not be exempt from regulatory requirements at any concentration, unless an application for exemption of a chemical mixture is submitted by a 4-piperidone manufacturer and the application is reviewed and accepted by DEA under 21 CFR 1310.13 (Exemption by Application Process). The control of chemical mixtures containing any amount of 4-piperidone is necessary to prevent the extraction, isolation, and use of 4-piperidone in the illicit manufacture fentanyl. This proposed rule would modify the Table of Concentration Limits in 21 CFR 1310.12(c) to reflect the fact that chemical mixtures containing any amount of 4-piperidone are subject to the CSA chemical control provisions.

## **Exemption by Application Process**

DEA has implemented an application process to exempt mixtures from the requirements of the CSA and its implementing regulations.<sup>14</sup> Under the application process, manufacturers may submit an application for exemption for those mixtures that do not qualify for automatic exemption. Exemption status can be granted if DEA determines that the mixture is formulated in such a way that it cannot be easily used in the illicit production of a controlled substance and that the listed chemical cannot be readily recovered.<sup>15</sup>

## **Requirements for Handling List I Chemicals**

If this rule is finalized as proposed, 4-piperidone will be subject to all of the regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, importing, and exporting of list I chemicals. Upon publication of a final rule, persons potentially handling 4-piperidone, including regulated chemical mixtures containing 4-piperidone, will be required to comply with list I chemical regulations, including the following:

1. *Registration.* Any person who manufactures, distributes, imports, or exports 4-piperidone, including chemical mixtures containing 4-piperidone, or proposes to engage in the manufacture, distribution, importation, or exportation of 4-piperidone, including chemical mixtures containing 4-piperidone, must obtain a registration pursuant to 21 U.S.C. 822, 823, 957, and 958. Regulations describing registration for list I chemical handlers are set forth in 21 CFR part 1309. DEA regulations require separate registrations for manufacturing, distributing, importing, and exporting of list I chemicals. 21 CFR 1309.21. Further, a separate registration is required for each principal place of business at one general physical location where list I chemicals are manufactured, distributed, imported, or exported by a person. 21 U.S.C. 822(e)(1) and 21 CFR 1309.23(a).

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<sup>14</sup> 21 CFR 1310.13.

<sup>15</sup> 21 CFR U.S.C. 802(39)(A)(vi).

DEA notes that under the CSA, “warehousemen” are not required to register and may lawfully possess list I chemicals, if the possession of those chemicals is in the usual course of business or employment. Under DEA implementing regulations, the warehouse in question must receive the list I chemical from a DEA registrant and shall only distribute the list I chemical back to the DEA registrant and registered location from which it was received. A warehouse that distributes list I chemicals to persons other than the registrant and registered location from which they were obtained is conducting distribution activities and is required to register as such.

Upon publication of a final rule, any person manufacturing, distributing, importing, or exporting 4-piperidone or a chemical mixture containing 4-piperidone would become subject to the registration requirement under the CSA. DEA recognizes, however, that it is not possible for persons who are subject to the registration requirements to immediately complete and submit an application for registration, and for DEA to immediately issue registrations for those activities. Therefore, to allow any continued legitimate commerce in 4-piperidone or a chemical mixture containing 4-piperidone, DEA is proposing to establish in 21 CFR 1310.09, a temporary exemption from the registration requirement for persons desiring to engage in activities with 4-piperidone or a chemical mixture containing 4-piperidone, provided that DEA receives a properly completed application for registration or application for exemption of a chemical mixture under 21 CFR 1310.13 on or before 30 days after publication of a final rule implementing regulations regarding 4-piperidone. The temporary exemption for such persons will remain in effect until DEA takes final action on their application for registration or application for exemption of a chemical mixture.

The temporary exemption applies solely to the registration requirement; all other chemical control requirements, including recordkeeping and reporting, would become effective on the effective date of the final rule. This is necessary because a delay in

regulating these transactions could result in increased diversion of chemicals desirable to drug traffickers.

Additionally, the temporary exemption for registration does not suspend applicable Federal criminal laws relating to 4-piperidone, nor does it supersede State or local laws or regulations. All handlers of 4-piperidone must comply with applicable State and local requirements in addition to the CSA regulatory controls.

2. *Records and Reports.* Every DEA registrant would be required to maintain records and submit reports with respect to 4-piperidone pursuant to 21 U.S.C. 830 and in accordance with 21 CFR part 1310.04 and 1310.05. Pursuant to 21 CFR 1310.04, a record must be kept for two years after the date of a transaction involving a listed chemical, provided the transaction is a regulated transaction.

Each regulated bulk manufacturer of a listed chemical will be required to submit manufacturing, inventory, and use data on an annual basis. 21 CFR 1310.05(d). Existing standard industry reports containing the required information are acceptable, provided the information is separate or readily retrievable from the report.

The CSA and its implementing regulations require that each regulated person must report to DEA any regulated transaction involving an extraordinary quantity of a listed chemical, an uncommon method of payment or delivery, or any other circumstance that the regulated person believes may indicate that the listed chemical will be used in violation of subchapter I of the CSA. In addition, regulated persons must report any proposed regulated transaction with a person whose description or other identifying characteristics DEA has previously furnished to the regulated person, any unusual or excessive loss or disappearance of a listed chemical under the control of the regulated person, and any in-transit loss in which the regulated person is the supplier. 21 U.S.C. 830(b) and 21 CFR 1310.05(a) and (b).

*Importation and Exportation.* All importation and exportation of 4-piperidone or a chemical

mixture containing 4-piperidone would need to be done in compliance with 21 U.S.C. 957, 958, and 971 and in accordance with 21 CFR part 1313.

3. *Security.* All applicants and registrants would be required to provide effective controls against theft and diversion of list I chemicals in accordance with 21 CFR 1309.71-1309.73.

4. *Administrative Inspection.* Places, including factories, warehouses, or other establishments and conveyances, where registrants or other regulated persons may lawfully hold, manufacture, distribute, or otherwise dispose of a list I chemical or where records relating to those activities are maintained, are controlled premises as defined in 21 U.S.C. 880(a) and 21 CFR 1316.02(c). The CSA allows for administrative inspections of these controlled premises as provided in 21 CFR part 1316, subpart A. 21 U.S.C. 880.

5. *Liability.* Any activity involving 4-piperidone not authorized by, or in violation of, the CSA, would be unlawful, and would subject the person to administrative, civil, and/or criminal action.

### **Solicitation for Information**

As part of this proposed rulemaking, DEA is soliciting information on any possible legitimate uses of 4-piperidone unrelated to fentanyl production (including industrial uses) in order to assess the potential economic impact of controlling 4-piperidone. DEA has searched information in the public domain for legitimate uses of this chemical, and has not documented a legitimate commercial or industrial use for 4-piperidone other than as an intermediary chemical in the production of fentanyl. DEA seeks, however, to document any unpublicized use(s) and other proprietary use(s) of 4-piperidone that are not in the public domain. Therefore, DEA is soliciting comment on the uses of 4-piperidone in the legitimate marketplace.

DEA is soliciting input from all potentially affected parties regarding: (1) The types of legitimate industries using 4-piperidone; (2) the legitimate uses of 4-piperidone, if any; (3)

the size of the domestic market for 4-piperidone; (4) the number of manufacturers of 4-piperidone; (5) the number of distributors of 4-piperidone; (6) the level of import and export of 4-piperidone; (7) the potential burden these proposed regulatory controls of 4-piperidone may have on any legitimate trade; (8) the potential number of individuals/firms that may be adversely affected by these proposed regulatory controls (particularly with respect to the impact on small businesses); and (9) any other information on the manner of manufacturing, distribution, consumption, storage, disposal, and uses of 4-piperidone by industry and others. DEA invites all interested parties to provide any information on any legitimate uses of 4-piperidone in industry, commerce, academia, research and development, or other applications. DEA seeks both quantitative and qualitative data.

### **Handling of Confidential or Proprietary Information**

Confidential or proprietary information may be submitted as part of a comment regarding this Notice of Proposed Rulemaking. Please see the “POSTING OF PUBLIC COMMENTS” section above for a discussion of the identification and redaction of confidential business information and personally identifying information.

### **Regulatory Analyses**

*Executive Orders 12866 and 13563, Regulatory Planning and Review, Improving and Regulation and Regulatory Review*

This proposed rule was developed in accordance with the principles of Executive Orders (E.O.) 12866 and 13563. E.O. 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, if regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health, and safety effects; distributive impacts; and equity). E.O. 13563 is supplemental to and reaffirms the principles, structures, and definitions governing regulatory review as established in E.O. 12866. E.O. 12866 classifies a “significant regulatory action,” requiring review by the Office of Management and Budget (OMB), as any regulatory action that is

likely to result in a rule that may: (1) have an annual effect on the economy of \$100 million or more or adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal Governments or communities; (2) create a serious inconsistency or otherwise interfere with an action taken or planned by another agency; (3) materially alter the budgetary impact of entitlements, grants, user fees, or loan programs or the rights and obligations of recipients thereof; or (4) raise novel legal or policy issues arising out of legal mandates, the President's priorities, or the principles set forth in the E.O.

A review of the 38 domestic suppliers of 4-piperidone indicates that 37 entities are not registered with DEA to handle list I chemicals. DEA anticipates that this proposed rule will impose minimal or no economic impact on affected entities; and thus, will not have a significant economic impact on any of the 37 affected small entities. Therefore, DEA has concluded that this proposed rule will not have a significant effect on a substantial number of small entities. If finalized as proposed, 4-piperidone will be subject to all of the regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, importing, and exporting of list I chemicals. 4-Piperidone is a precursor chemical used in, and is important to, the illicit manufacture of the schedule II controlled substance fentanyl. The distribution of illicitly manufactured fentanyl has caused an unprecedented outbreak of thousands of fentanyl-related overdoses in the United States in recent years.

DEA has searched information in the public domain for any legitimate uses of 4-piperidone, and has not documented a use for 4-piperidone other than as an intermediary chemical in the production of fentanyl. Based on the review of import and quota information for NPP, ANPP, and fentanyl, DEA believes the vast majority of, if not all, legitimate pharmaceutical fentanyl is produced via a synthetic route involving NPP and ANPP as intermediaries. The quantities of NPP indicated in import data and quantities of ANPP



indicated in import and quota data generally correspond with the quantities of legitimate pharmaceutical fentanyl produced in the United States. Therefore, DEA concludes the vast majority of, if not all, 4-piperidone undergoing chemical transactions is being used for the manufacturing of illicit fentanyl. DEA cannot rule out the possibility that minimal quantities of 4-piperidone is being used for the manufacturing of legitimate pharmaceutical fentanyl. However, if there are any quantities of 4-piperidone used for the manufacturing of legitimate pharmaceutical fentanyl, the quantities are believed to be small and economically insignificant. DEA welcomes any public comment on these quantities and their economic significance.

DEA evaluated the costs and benefits of this proposed action.

#### Costs

DEA believes the market for 4-piperidone for the legitimate manufacturing of pharmaceutical fentanyl is minimal. As stated above, the only use for 4-piperidone of which DEA is aware is as an intermediary for the manufacturing of fentanyl. Any manufacturer, distributor, importer, or exporter of 4-piperidone for the production of legitimate pharmaceutical fentanyl, if they exist at all, would incur costs if this proposed rule were finalized. The primary costs associated with this proposed rule would be the annual registration fees for list I chemicals (\$3,699 for manufacturers and \$1,850 for distributors, importers, and exporters). However, any manufacturer that uses 4-piperidone for legitimate pharmaceutical fentanyl production would already be registered with DEA and have all security and other handling processes in place because of the controls already in place on fentanyl, resulting in minimal cost to those entities. While different forms of handling the scheduled substance versus the list I chemical (distribution of fentanyl vs exporting 4-piperidone) could require a separate registration for the different handling of the substances, if an entity is already registered to handle, manufacture, import, or export a scheduled substance, the entity would not need an additional registration for the list I chemical,

provided it is handling the list I chemical in the same manner that it is registered for with the scheduled substance, or as a coincident activity permitted by §1309.21. Even with the possibility of these additional registrations, DEA believes that the cost will be minimal.

DEA has identified 38 domestic suppliers of 4-piperidone. Only one is registered to handle list I chemicals, the remaining 37 are not registered with DEA to handle list I chemicals. It is difficult to estimate how much 4-piperidone is distributed by these suppliers. It is common for chemical distributors to have items in their catalog while not actually having any material level of sales. Based on the review of import and quota information for NPP, ANPP, and fentanyl, where the quantities of NPP and ANPP imported and manufactured generally correspond with the quantities of fentanyl produced, DEA believes any quantity of sales from these distributors for legitimate pharmaceutical fentanyl manufacturing is minimal. If this proposed rule is finalized, suppliers for the legitimate use of 4-piperidone are expected to choose the least-cost option, and stop selling the minimal quantities, if any, of 4-piperidone, rather than incur the registration cost. Because DEA believes the quantities of 4-piperidone supplied for the legitimate manufacturing of pharmaceutical fentanyl are minimal, DEA estimates that the cost of foregone sales is minimal; and thus, the cost of this proposed rule is minimal. DEA welcomes any public comment regarding this estimate.

This analysis excludes consideration of any economic impact to those businesses that facilitate the manufacturing and distribution of 4-piperidone for the manufacturing of illicit fentanyl. As a law enforcement organization and as a matter of principle, DEA believes considering the economic utility of facilitating the manufacture of illicit fentanyl would be improper.

#### Benefits

Controlling 4-piperidone is expected to prevent, curtail, and limit the unlawful manufacture and distribution of the controlled substance, fentanyl. As a list I chemical,

handling of 4-piperidone would require registration with DEA and various controls and monitoring as required by the CSA. This proposed rule is also expected to assist preventing the possible theft or diversion of 4-piperidone from any legitimate firms. DEA also believes control is necessary to prevent unscrupulous chemists from synthesizing 4-piperidone and selling it (as an unregulated material) through the Internet and other channels, to individuals who may wish to acquire unregulated intermediary chemicals for the purpose of illicitly manufacturing fentanyl.

In summary, DEA conducted a qualitative analysis of costs and benefits. DEA believes this proposed action, if finalized, will minimize the diversion of 4-piperidone. DEA believes the market for 4-piperidone for the legitimate manufacturing of pharmaceutical fentanyl is minimal. Therefore, any potential cost as a result of this regulation is minimal.

#### *Executive Order 12988, Civil Justice Reform*

This proposed regulation meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988 Civil Justice Reform to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

#### *Executive Order 13132, Federalism*

This proposed rulemaking does not have federalism implications warranting the application of E.O. 13132. The proposed rule does not have substantial direct effects on the States, on the relationship between the national Government and the States, or the distribution of power and responsibilities among the various levels of government.

#### *Executive Order 13175, Consultation and Coordination with Indian Tribal Governments*

This proposed rule does not have tribal implications warranting the application of E.O. 13175. This proposed rule does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on

the distribution of power and responsibilities between the Federal Government and Indian tribes.

### *Regulatory Flexibility Act*

The Administrator, in accordance with the Regulatory Flexibility Act (5 U.S.C. 601-612), has reviewed this proposed rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities. As discussed above, if finalized as proposed, 4-piperidone or a chemical mixture containing 4-piperidone will be subject to all of the regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, importing, and exporting of list I chemicals. 4-Piperidone is a precursor chemical used in, and is important to, the illicit manufacture of the schedule II controlled substance fentanyl. The distribution of illicitly manufactured fentanyl has caused an unprecedented outbreak of thousands of fentanyl-related overdoses in the United States in recent years. DEA has not identified any legitimate industrial use for 4-piperidone other than its role as an intermediary chemical in the production of fentanyl. However, DEA believes the vast majority, if not all, of legitimate pharmaceutical fentanyl is produced via a synthetic route involving NPP and ANPP as intermediaries, not 4-piperidone. The review of import and quota information for fentanyl, ANPP, and NPP supports this belief. Therefore, DEA believes the vast majority, if not all, of 4-piperidone is used for the illicit manufacturing of fentanyl. The primary costs associated with this proposed rule are the annual registration fees (\$3,699 for manufacturers and \$1,850 for distributors, importers, and exporters). Additionally, any manufacturer that uses 4-piperidone for legitimate pharmaceutical fentanyl production would already be registered with DEA and have all security and other handling processes in place, resulting in minimal cost. DEA has identified 38 domestic suppliers of 4-piperidone, 37 of which are not registered with DEA to handle list I chemicals. All non-registered domestic suppliers are affected and are estimated to be small entities (based on Small Business Administration size standard for chemical distributors and

Statistics of U.S. Business data).<sup>16</sup> It is impossible to know how much 4-piperidone is distributed by these suppliers. It is common for chemical distributors to have items in their catalog while not actually having any material level of sales. Based on the review of import and quota information for NPP, ANPP, and fentanyl, where the quantities of NPP and ANPP imported and manufactured generally correspond with the quantities of fentanyl produced, DEA believes any quantity of sales from these distributors for legitimate pharmaceutical fentanyl manufacturing is minimal. Therefore, DEA estimates the cost of this rule on any affected small entity is minimal. DEA welcomes any public comment regarding this estimate. Based on these factors, DEA projects that this rule, if promulgated, will not result in a significant economic impact on a substantial number of small entities.

#### *Unfunded Mandates Reform Act of 1995*

On the basis of information contained in the “Regulatory Flexibility Act” section above, DEA has determined and certifies pursuant to the Unfunded Mandates Reform Act of 1995 (UMRA), 2 U.S.C. 1501 *et seq.*, that this action would not result in any Federal mandate that may result “in the expenditure by State, local, and tribal Governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted for inflation) in any one year . . . .” Therefore, neither a Small Government Agency Plan nor any other action is required under provisions of UMRA.

#### *Paperwork Reduction Act*

This proposed action does not impose a new collection of information requirement under the Paperwork Reduction Act, 44 U.S.C. 3501-3521. This proposed action would not impose recordkeeping or reporting requirements on State or local Governments, individuals, businesses, or organizations. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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<sup>16</sup> <https://www.sba.gov/sites/default/files/2018-07/NAICS%202017%20Table%20of%20Size%20Standards.pdf>.

**List of Subjects in 21 CFR part 1310**

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, DEA proposes to amend 21 CFR part 1310 as follows:

**PART 1310— RECORDS AND REPORTS OF LISTED CHEMICALS AND CERTAIN MACHINES; IMPORTATION AND EXPORTATION OF CERTAIN MACHINES**

1. The authority citation for 21 CFR part 1310 continues to read as follows:

**Authority:** 21 U.S.C. 802, 827(h), 830, 871(b), 890.

2. In §1310.02, add paragraph (a)(38) to read as follows:

**§ 1310.02 Substances covered.**

\* \* \* \* \*

(a) \* \* \*

(38) 4-piperidone (piperidin-4-one), its acetals, its amides, its carbamates, its salts, and salts of its acetals, its amides, and its carbamates, whenever the existence of such is possible.....8330

\* \* \* \* \*

3. In §1310.04:

a. Redesignate paragraphs (g)(1)(xvi) and (xvii) as paragraphs (g)(1)(xvii) and (xviii) respectively; and

b. Add a new paragraph (g)(1)(xvi).

The revision reads as follows:

**§ 1310.04 Maintenance of records.**

\* \* \* \* \*

(g) \* \* \*

(1) \* \* \*

(xvi) 4-piperidone (piperidin-4-one), its acetals, its amides, its carbamates, its salts, and salts of its acetals, its amides, and its carbamates, whenever the existence of such is possible

\* \* \* \* \*

4. In § 1310.09, add paragraph (s) to read as follows:

**§1310.09 Temporary exemption from registration.**

\* \* \* \* \*

(s)(1) Each person required under 21 U.S.C. 822 and 21 U.S.C. 957 to obtain a registration to manufacture, distribute, import, or export regulated 4-piperidone (piperidin-4-one), its acetals, its amides, its carbamates, its salts, and salts of its acetals, its amides, and its carbamates, whenever the existence of such is possible, including regulated chemical mixtures pursuant to § 1310.12, is temporarily exempted from the registration requirement, provided that DEA receives a properly completed application for registration or application for exemption for a chemical mixture containing 4-piperidone pursuant to § 1310.13 on or before 30 days after the publication of a rule finalizing this action. The exemption would remain in effect for each person who has made such application until the Administration has approved or denied that application. This exemption applies only to registration; all other chemical control requirements set forth in the Act and parts 1309, 1310, 1313, and 1316 of this chapter remain in full force and effect.

(2) Any person who manufactures, distributes, imports, or exports a chemical mixture containing 4-piperidone (piperidin-4-one), its acetals, its amides, its carbamates, its salts, and salts of its acetals, its amides, and its carbamates, whenever the existence of such is possible whose application for exemption is subsequently denied by DEA must obtain a registration with DEA. A temporary exemption from the registration requirement will also be provided for those persons whose application for exemption is denied, provided that DEA receives a properly completed application for registration on or before 30 days following the

date of official DEA notification that the application for exemption has been denied. The temporary exemption for such persons will remain in effect until DEA takes final action on their registration application.

5. In 1310.12(c), amend the table by adding in alphabetical order an entry for “4-piperidone (piperidin-4-one), its acetals, its amides, its carbamates, its salts, and salts of its acetals, its amides, and its carbamates, whenever the existence of such is possible” to read as follows:

**§ 1310.12 Exempt chemical mixtures.**

\* \* \* \* \*

(c) \* \* \*

**Table of Concentration Limits**

	DEA chemical code number	Concentration	Special conditions
List I Chemicals			
* * * * *			
4-piperidone (piperidin-4-one), its acetals, its amides, its carbamates, its salts, and salts of its acetals, its amides, and its carbamates, whenever the existence of such is possible	8330	Not exempt at any concentration	Chemical mixtures containing any amount of 4-piperidone are not exempt
* * * * *			

\* \* \* \* \*

**Signing Authority**

This document of the Drug Enforcement Administration was signed on September 8, 2022, by Administrator Anne Milgram. That document with the original signature and date is maintained by DEA. For administrative purposes only, and in compliance with requirements of the Office of the Federal Register, the undersigned DEA Federal Register Liaison Officer



has been authorized to sign and submit the document in electronic format for publication, as an official document of DEA. This administrative process in no way alters the legal effect of this document upon publication in the Federal Register.

**Scott Brinks,**  
Federal Register Liaison Officer,  
Drug Enforcement Administration.

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